the PTO. The information contained in the computer readable disc is identical to that of the paper copy. This amendment contains no new matter. Applicant submits that this amendment, the accompanying computer readable sequence listing, and the paper copy thereof serve to place this application in a condition of adherence to the rules 37 C.F.R. § 1.821-1.825.

Rejections Under 35 U.S.C. § 112, second paragraph

Claims 19-31 and 33-40 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for not reciting the positional relationship of the various components comprising the test chamber. Applicants submit that the specification makes clear the positional relationship of the various components to each other. For example, page 74, lines 21-29 state:

> Accordingly, the present invention further provides apparatus for the detection of nucleic acids using AC detection methods. The apparatus includes a test chamber which has at least a first measuring or sample electrode, and a second measuring or counter electrode. Three electrode systems are also useful. The first and second measuring electrodes are in contact with a test sample receiving region, such that in the presence of a liquid test sample, the two electrodes may be in electrical contact.
>
> In a preferred embodiment, the first measuring electrode comprises a single stranded nucleic acid covalently attached via a spacer, and preferably via a conductive oligomer, such as are described herein.

As to the relationship of the electrode and the passivation agent, the specification on page 35, lines 18-19 states:

> In a preferred embodiment, the electrode further comprises a passavation agent, preferably in the form of a monolayer on the electrode surface.

And the positional relationship of the AC/DC voltage source is found on page 75, lines 5-7:

> The apparatus further comprises an AC voltage source electrically connected to the test chamber; that is, to the measuring electrodes. Preferably, the AC voltage source is capable of delivering DC offset voltage as well.

The claim has been amended to make it clear that the AC/DC voltage source is attached to the measuring electrodes. This amendment, long with the description of the relationship of various components to each other found in the specification should obviate the rejection.

Claims 19-31 and 33-40 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite in the recitation of "passivation agent monolayer." Applicants submit the specification on page 35, lines 18-19 describes the nature of the attachment of the passivation agent monolayer to the electrode:

> In a preferred embodiment, the electrode further comprises a passavation agent, preferably in the form of a monolayer on the electrode surface.

On page 35, line 21 through page 38, line 2, a passivation monolayer is defined:

> A passavation agent layer facilitates the maintenance of the nucleic acid away from the electrode surface. In addition, a passavation agent serves to keep charge carriers away from the surface of the electrode. Thus, this layer helps to prevent electrical contact between the electrodes and the electron transfer moieties, or between the electrode and charged species within the solvent. Such contact can result in a direct "short circuit" or an indirect short circuit via charged species which may be present in the sample. Accordingly, the monolayer of passavation agents is preferably tightly packed in a uniform layer on the electrode surface, such that a minimum of "holes" exist. Alternatively, the passavation agent may not be in the form of a monolayer, but may be present to help the packing of the conductive oligomers or other characteristics.

> The passavation agents thus serve as a physical barrier to block solvent accesibility to the electrode. As such, the passavation agents themselves may in fact be either (1) conducting or (2) nonconducting, i.e. insulating, molecules. Thus, in one embodiment, the passavation agents are conductive oligomers, as described herein, with or without a terminal group to block or decrease the transfer of charge to the electrode. Other passavation agents which may be conductive include oligomers of $-(CF_2)_n-$, $-(CHF)_n-$ and $-(CFR)_n-$. In a preferred embodiment, the passavation agents are insulator moieties.

To summarize, a passivation agent monolayer is generally attached to the electrode in the same manner as a conductive oligomer. When the passivation agent is arranged in a uniform layer on the electrode surface, it is referred to as a passivation agent monolayer. Accordingly, applicants submit what is meant by a passivation monolayer is not indefinite and request withdrawal of the rejection.

Claims 19-31 and 33-40 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite in the location of the electron transfer moieties. As explained in the specification on page 46, lines 4-12 ,electron transfer moieties may be located at the following positions:

> As described herein, the invention provides compositions containing electrodes as a first electron transfer moiety linked via a conductive oligomer to a nucleic acid which has at least a second electron transfer moiety covalently attached. Any combination of positions of electron transfer moiety attachment can be made; i.e. an electrode at the 5' terminus, a second electron transfer moiety at an internal position; electrode at the 5' terminus, second moiety at the 3' end; second moiety at the 5' terminus, electrode at an internal position; both electrode and second moiety at internal positions; electrode at an internal position, second moiety at the 3' terminus, etc. A preferred embodiment utilizes both the electrode and the second electron transfer moiety attached to internal nucleosides.

As is made clear in the specification and in the claims in which electron transfer moieties are claimed, electron transfer moieties may be attached to a nucleic acid in a

variety of positions. Accordingly, applicants submit the claims are not indefinite and request withdrawal of the rejection.

Rejection under 35 U.S.C. §102(e)

Claims 19-31 and 33-40 are rejected under 35 U.S.C. §102(e) as being anticipated by Ribi et al., (the '568 patent).

As stated previously, the present invention is directed to compositions and methods useful in the detection of nucleic acids utilizing electron transfer mechanisms. The invention relies on electron transfer between electron donor and acceptor groups (electron transfer moieties or ETMs) present in a nucleic acid hybridization complex and an electrode. Thus, the invention utilizes an electrode with a covalently attached nucleic acid. Upon hybridization with a target sequence, a double-stranded nucleic acid hybridization complex forms that contains an ETM. Detection proceeds with the input of an AC signal resulting in electron transfer between the ETM and the electrode.

Ribi et al. describes a system that utilizes at least four components: a substrate, a pair of interdigitating electrodes, a polymerizable surfactant film that forms a crystalline structure, and at least one binding ligand ("a member of a specific binding pair").

Ribi's substrate is an insulating solid support or substrate (see column 3, line 19), and can be made of a variety of materials. Preferred embodiments utilize polystyrene (see column 4, line 36). It should be noted that polystyrene is not a conductive material, and is not used in Ribi et al. as such.

Ribi's sensor, referring to Ribi's Fig. 4, consists of this insulating substrate (10), upon the surface of which are two electrodes (30). Between these two electrodes is the conducting file (36) "so that changes in the electrical characteristics of the film 36 are

readily detected by an external circuit." (see column 24, lines 41-43). Thus, the conducting film itself closes or completes the electrical circuit, not the "attaching the nucleic acids" as the examiner asserts. In fact, the circuit is complete whether or not any nucleic acid is attached. Rather, the nucleic acids are attached to the conducting polymer (not the electrode) through linkers so that binding of an analyte to the nucleic acids will result in a change in the conductivity of the conducting polymer. This change in conductivity is measured with the two electrodes by passing an electrical current through the already completed circuit. Ribi et al. The electrodes (30) are "coated with an electrically inert sealant layer 36 which prevents contact between the electrodes 16 and any aqueous medium in the channel 32." The purpose of this sealant is to ensure that the electrical current, which is applied to measure the conductivity of the polymer layer, passes only through the polymer layer and not through the aqueous medium.

A "highly oriented polymerized surfactant film" (column 3, lines 19-20) is then formed on the insulative substrate. This may be done covalently or non-covalently (see column 3, lines 37-41). This surfactant film is either electronically semi-conducting or variably conducting (see column 3, lines 21-22).

Binding members (i.e. for binding a target analyte) are then attached to the surfactant film (sometimes also referred to in Ribi et al. as a lipid portion; see column 5, line 26). The binding members are generally added to the surfactant film by using a linker (see column 5, lines 25-56). These linkers are chosen depending on the "degree to which one wishes to perturb the electrical properties of the polymer" (see column 5, line 34-36). That is, as shown below, the mechanism of Ribi et al. relies on a change in the electromagnetic (electrical or optical) properties of the film as a result of the binding of a target analyte. Thus, Ribi et al. states that "[t]he more rigid and shorter the linker,

assuming high affinity analyte binding, the greater the perturbation of the polymer upon binding of the specific binding member to its complementary member." (Column 5, lines 37-40).

In addition, this perturbation causes a change in the electrical properties of the surfactant due to the presence of dopants. These dopants (donors and acceptors) alter their orientation in response to the binding of the target analytes, thus causing the changes in the electrical properties of the film. See column 5, lines 59-64:

> The orientation of the acceptor or donor molecule (dopant) with respect to the polymer lattice will affect the polymers' net electrical characteristics. The electrical properties of the film will be affected by analyte binding where the binding event causes a change in the orientation of the dopant molecule.

Generally, Ribi et al. functions in the following way: Upon binding of a target analyte, the electromagnetic properties of the film change (either its electronic or optical properties; see column 3, line 26) as a result of binding of a target analyte for detection. Therefore, the film is the intervening medium between the two electrodes, and changes in the film's properties serve as the basis of the assay for the presence or absence of the target analyte.

Furthermore, in order to make this work (as shown in Figure 3, column 16, lines 27-31, and column 16, line 61 to column 17, line 42 ("Electrode Protection") of Ribi et al.), the electrodes must be electrically insulated from the aqueous medium using such things as parafilm, wax, nail polish, etc., so that direct electrical contact of two interdigitating electrodes does not occur. As the Examiner will appreciate, if there is direct electrical contact of the two electrodes through the aqueous media, the presence of charge carriers in the sample would provide two pathways for current flow: through the solution and through the film. Presumably this would be unacceptable.

As outlined above, Ribi et al. does not teach or suggest the compositions of the present invention. The present invention has conductive oligomers attached to both an electrode and the binding ligand, e.g. a nucleic acid. Ribi et al. does not outline, anywhere in the specification, covalent attachment of a conductive oligomer to the electrode; rather, in Ribi et al., the surfactant is attached, either covalently or non-covalently, to the

insulative substrate. Ribi et al. describes formation of the electrodes at column 5, lines 5-14, column 27, lines 5-10, and column 10, lines 17-31. The electrodes are either formed on the substrate prior to attachment of the conductive polymer to the substrate or are applied on top of the conductive polymer after its attachment. As will be appreciated in the art, Ribi's disclosed methods of forming electrodes on the surfaces are non-covalent methods such as "painting" the electrodes onto the substrate (see the Examples, column 27, lines 5-10) and photoresist/etching methods (see column 10, lines 17-31).

In addition, the present invention does not rely on a change in conductivity of the conductive oligomers as a result of binding of a target analyte for detection. That is, the conductive oligomers of the invention do not change their conductivity as a result of analyte binding. Rather, the present invention relies on electron transfer between the ETMs of the invention and the electrode.

As the Examiner is aware, the law is well established that in order to anticipate a claim, the prior art must disclose "each and every element"of the claimed invention. SSIH Equipment S.A.v. U.S. Inc. Int'l. Trade Commission, 218 USPQ 678, 688 (Fed. Cir. 1983). As stated by the Federal Circuit in In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990), "[f]or a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of the claimed invention must be identically shown in a single reference." (Emphasis added). See also Glaverbel Societe Anonyme v. Northlake Marketing & Supply, Inc., 33 USPQ2d 1496 (Fed. Cir. 1995).

Ribi et al. does not disclose either the covalent attachment of nucleic acids to the electrode or the use of monolayers. Accordingly, the rejection is improper and should be withdrawn.

Rejection under 35 U.S.C. §103

Claims 19-34 are rejected under 35 U.S.C. §103 as being obvious over Ribi et al.

As stated in M.P.E.P. §2142, a *prima facie* case of obviousness requires three basic criteria to be met. First, there must be some suggestion or motivation to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the references, taken alone or in combination, must teach or suggest all the claim limitations.

The applicants submit that Ribi does not provide any motivation or suggestion to

practice the claimed invention. There simply is no motivation to covalently attach the nucleic acids to the electrode. In fact, Ribi et al. actually teaches away from this, as it is important to the Ribi invention that the electrodes must be electrically insulated from the aqueous medium containing the target analyte for binding to the binding member. Having the binding member directly on the electrode would not allow this electrical insulation. Thus Ribi actually teaches away from practicing the invention. As stated in M.P.E.P. §2143.01:

> If [the] proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. In re Gordon, 221 USPQ 1125 (Fed. Cir. 1984).

Similarly, a reference which leads one of ordinary skill in the art away from the claimed invention cannot render the claimed invention unpatentably obvious. Dow Chemical Co. v. American Cyanamid Co., 2 USPQ 2d 1350 (Fed. Cir. 1987).

Therefore, Ribi et al. does not provide the required motivation to combine. Thus a *prima facie* case of obviousness has not been made and the rejection is improper.

Even assuming, arguendo, that the required motivation exists, Ribi et al. does not provide a reasonable expectation of success. As argued above, the attachment of the nucleic acid to the electrode does not give a reasonable expectation of success. Accordingly, a *prima facie* case of obviousness has not been made and the rejection is improper.

Finally, Ribi et al. does not teach or suggest all of the claim elements, including the covalent attachment of the nucleic acid to the electrode. Accordingly, a *prima facie* case of obviousness has not been made and the rejection is improper.

Accordingly, the rejection under 35 U.S.C. §103 should be withdrawn.

The applicants submit that the claims are now in condition for allowance and an early notification of such is respectfully solicited. If after review, the Examiner feels that there are further unresolved issues, the Examiner is invited to call the undersigned at (415) 781-1989.

The Commissioner is authorized to charge any additional fees which may be required, including extension fees or other relief which may be required, or credit any overpayment to Deposit Account No. 06-1300 (Our Order No. A-64558-1/RFT/ RMS /RMK).

Respectfully submitted,

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Dated: 9/13/00
1027617.RMK

APPENDIX OF PENDING CLAIMS

19. (Twice Amended) An apparatus for the detection of target nucleic acids in a test sample, comprising:

a) a test chamber comprising a first and a second electrode, wherein said first electrode comprises a single stranded nucleic acid covalently attached to said electrode via a spacer, wherein said electrode further comprises a passivation agent monolayer; and

b) an AC/DC voltage source electrically connected to said test chamber.

20. (Twice Amended) An apparatus for the detection of target nucleic acids in a test sample, comprising:

a) a test chamber comprising a first and a second electrode, wherein said first electrode comprises a covalently attached single stranded nucleic acid, wherein said electrode further comprises a passivation agent monolayer and wherein said nucleic acid further comprises a covalently attached second electron transfer moiety; and

b) an AC/DC voltage source electrically connected to said test chamber.

21. An apparatus according to claim 19, 20 or 26, further comprising:

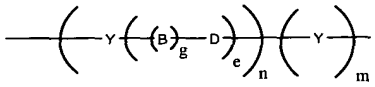
d) a processor coupled to said electrodes.

22. (Amended) An apparatus according to claim 19, 20 or 26, wherein said AC voltage source is capable of delivering frequencies from between about 1 Hz to about 100 kHz.

23. (Twice Amended) An apparatus according to claim 20, wherein said single stranded nucleic acid is covalently attached to said first electrode via a spacer.

24. An apparatus according to claim 23, wherein said spacer is a conductive oligomer.

25. (Twice Amended) An apparatus according to claim 19, 23 or 27, wherein said spacer is a conductive oligomer having the formula:



wherein

Y is an aromatic group;

n is an integer from 1 to 50;

g is either 1 or zero;

e is an integer from zero to 10; and

m is zero or 1;

wherein when g is 1, B-D comprises two atoms forming a bond able to conjugate with neighboring bonds; and

wherein when g is zero, e is 1 and D is selected from the group consisting of carbonyl and a heteroatom moiety, wherein the heteroatom is selected from oxygen, sulfur, nitrogen and phosphorus.

3 26. (Amended) An apparatus for the detection of target nucleic acids in a test sample, comprising:

a) a test chamber comprising a first and a second electrode, wherein said first electrode comprises a covalently attached first single stranded nucleic acid and a passivation agent monolayer;

b) a second nucleic acid covalently attached to a electron transfer moiety; and

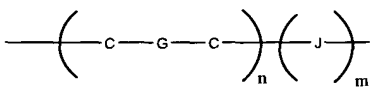
c) an AC/DC voltage source electrically connected to said test chamber.

9 27. (Amended) An apparatus according to claim 26 wherein said single stranded nucleic acid is covalently attached to said electrode via a spacer.

10 28. An apparatus according to claim 27, wherein said spacer is a conductive oligomer.

11 29. An apparatus according to claim 27, wherein said spacer is an insulator.

12 30. (Amended) An apparatus according to claim 19, 23 or 27, wherein said spacer is a conductive oligomer having the formula:



wherein

C are carbon atoms;

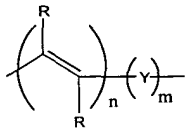
n is an integer from 1 to 50;

m is 0 or 1;

J is a heteroatom selected from the group consisting of nitrogen, silicon, phosphorus, sulfur, carbonyl and sulfoxide; and

G is a bond selected from single, double and triple bonds.

31. (Amended) An apparatus according to claim 19, 23 or 27, wherein said spacer is a conductive oligomer having the formula:



wherein

n is an integer from 1 to 50;

m is either zero or 1;

Y is an aromatic group; and

R is a substitution group.

33. (Amended) An apparatus according to claim 19, 20 or 26 wherein said passivation agent monolayer comprises conductive oligomers.

34. (Amended) An apparatus according to claim 19, 20 or 26 wherein said passivation agent monolayer comprises insulators.